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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,829	KHAN, SHAHARYAR	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-127* is/are pending in the application.

4a) Of the above claim(s) *116,120 and 122-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114,115,117-119 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 115 and 118, is acknowledged. The traversal is on the ground(s) that the examiner improperly applied unity of invention rules and that the U.S. patent rules do not apply to a national stage of a 371 application. The assertion is simply false. Under 35 U.S.C. 372(b)(2), "IN CASE OF INTERNATIONAL APPLICATIONS DESIGNATING BUT NOT ORIGNINATING IN, THE UNITED STATES…THE COMMISSIONER MAY CAUSE THE QUESTION OF UNITY OF INVENTION TO BE REEXAMINED UNDER SECTION 121 OF THIS TITLE, WITHIN THE SCOPE OF THE REQUIREMENTS OF THE TREATY AND THE REGULATIONS;…" Therefore, it is proper to apply rules as defined in 35 U.S.C. 121 and 372(b)(2) in a national stage of 371 application.

The applicant then argues that groups are linked by the discovery of applicant of compositions for introducing polynucleotides into a cell without using receptor mediated localization techniques and targeting the polynucleotide to specific organelles.

The argument has been fully considered but found not persuasive. 37 CFR 1.475 (a) indicates "AN INTERNATIONAL AND A NATIONAL STAGE APPLICATION SHALL RELATED TO ONE INVENTION ONLY OR TO A GROUP OF INVENTIONS SO LINKED AS TO FORM A SINGLE GENERAL INVENTIVE CONCEPT ('REQUIREMENT OF UNITY OF INVENTION'). 37 CFR 1.475 (b) states "AN INTERNATIONAL OR A NATIONAL STAGE APPLICATION CONTAINING CLAIMS TO DIFFERENT CATEGORIES OF INVENTION WILL BE CONSIDERED TO HAVE UNITY OF INVENTION IF THE CLAIMS ARE DRAWN **ONLY TO ONE** OF THE FOLLOWING COMBINATIONS OF CATEGORIES: (1) A PRODUCT AND A PROCESS SPECIALLY ADAPTED FOR THE MANUFACTURE OF SAID PRODUCT; OR (2) A PRODUCT AND A PROCESS

OF USE OF SAID PRODUCT; …". 37 CFR 1.475 (b) does not provide for more than one product as a combination of the invention.

37 CFR 1.475 (a) also indicates "WHERE A GROUP OF INVENTIONS IS CLAIMED IN AN APPLICATION, THE REQUIREMENT OF UNITY OF INVENTION SHALL BE FULFILLED ONLY WHEN THERE IS A TECHNICAL RELATIONSHIP AMONG THOSE INVENTIONS INVOLVING ONE OR MORE OF THE SAME OR CORRESPONDING **SPECIAL TECHNICAL FEATURES**." The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant case, as stated in the restriction requirement different vectors are structurally different and different processes use structural different agents. The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT 13.2, they lack the same or corresponding special technical features for the following reasons: as cited in the instant Office action that follows, *Yang et al*. (FEBS 2002;532:36-44), in view of *Balzan et al*. (PNAS 1995;92:4219-23) and *Robbins et al*. (Pharmacol Ther 1998;80:35-47) render obvious over claim 118 but not claims 116 and 125. Consequently, the special technical feature which links claims 114-127 does not provide a contribution over the prior art as a whole, so unity of invention is lacking and restriction is appropriate.

Therefore, it is maintained that these inventions are distinct due to their divergent subject matter and are thus, separately classified and searched. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 114-127 are pending. Claims 116, 120, 122-127 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 114, 115, 117-119 and 121 are under current examination.

Specification

The abstract of the disclosure is objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b). The cover page of a PCT publication is no longer acceptable by the Patent publication branch at the USPTO.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g. Specification, page 21, line 24; page 30, line 5). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is objected to because some texts in table I appear to have been cut off due to the width of the table. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 114, 115, 117-119 and 121 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim (114) recitation "wherein the recombinant polypeptide is operably lined to a polynucleotide". It is unclear how a polypeptide could operably linked to a polynucleotide, and hence the metes and bounds of the claims are unclear.

In view of the disclosure of the specification, for the sake of a compact prosecution and for the purpose of apply prior art, the claims have been interpreted as drawn to a composition comprising a polynucleotide sequence encoding a recombinant polypeptide, wherein the recombinant polypeptide comprises an organelle localization signal operably linked to a protein transduction domain and a heterologous protein (encoded by a polynucleotide).

Claim Rejections - 35 USC § 102

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 114, 117, 119, 121 are rejected under 35 U.S.C. 102(a) as being anticipated by *Del Gaizo et al*. (Mole Ther 2003 Jun;7:720-30, IDS).

Del Gaizo teaches a composition comprising an expression vector expressing a recombinant fusion protein having a mitochondria localization signal sequence (mitochondrial malate dehydrogenase signal sequence, mMDH) linked to a TAT protein transduction domain, and a eGFP (e.g. figure 1). *Del Gaizo* teaches expressing the fusion protein in various cells *in vitro* and *in vivo* (e.g. figures 2, 4, 6). Accordingly, *Del Gaizo* anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 114, 117, 119, 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Yang et al*. (FEBS 2002;532:36-44), in view of *Balzan et al*. (PNAS 1995;92:4219-23).

Yang teaches that increasing evidence in the art had shown that TAT protein (a protein transduction domain) is capable of mediating heterologous protein across the plasma membrane into nearly all eukayotic cells, which is important for efficient intracellular delivery of a heterologous protein. *Yang* discloses an expression vector comprising a nucleic acid encoding an 11 amino acids of the TAT (PTD = instant SEQ ID No: 3, e.g. column 2, page 36) fused in-frame with GFP or Smac, wherein the TAT fusion protein confers more efficient protein internalization and its subsequent

subcellular (organelle) localization (e.g. the introduction, figure 3). *Yang* teaches expressing the fusion protein in *E. Coli* cells (e.g. the abstract). *Yang* also teaches that different delivery approach may have caused the expression in different subcellular locations (cytosol or nucleus). *Yang* does not teach to include an organelle localization signal in the delivery construct.

Balzan supplemented *Young* by establishing it was known in the art before instant filing date for targeting a heterologous protein to mitochondria using a targeting presequence. *Balzan* teaches using a yeast manganese superoxide dismutase (Mn=instant SEQ ID No: 62) for targeting the FeSOD protein to mitochondria, without the pre-sequence, the FeSOD would express in cytosol (e.g. see discussion section).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector as taught by *Yang* by simply including the mitochondria targeting sequence Mn as taught by *Balzan* with a reasonable expectation of success when mitochondria-restricted expression is so desired. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified vector would have efficient membrane transfer and subcellular organelle-specific targeting, suitable for mitochondria delivery of a heterologous protein. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 115 and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Yang et al*. (FEBS 2002;532:36-44), in view of *Balzan et al*. (PNAS 1995;92:4219-

23) as applied to 114, 117, 119, 121 above, further in view of *Robbins et al*. (Pharmacol Ther 1998;80:35-47).

Claim 118 is directed to a viral particle composition comprising the recombinant polynucleotide. The combined teaching of *Yang* in view of *Balzan* teaches a plasmid vector, not a viral vector for delivery of a heterologous protein.

Robbins supplemented *Yang* in view of *Balzan* by establishing it was known in the art that various viral vectors were well known in the art for efficient gene transfer *in vitro* and *in vivo* (see relevant sections). *Robbins* teaches a viral vector generally have higer transduction efficiency than a plasmid vector.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the vector as taught by *Yang* in view of *Balzan* for intracellular delivering a mitochondria protein with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the vector taught by the combined teaching would have more efficient cellular transduction, membrane transfer and mitochondria-specific targeting function. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 119 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Yang et al*. (FEBS 2002;532:36-44), in view of *Balzan et al*. (PNAS 1995;92:4219-23) as applied to 114, 117, 119, 121 above, further in view of *Hashimoto et al*. (Biochem Biophys Res Comm 2001;283:460-8) and *Maximov* (Med Hypotheses 2002;59:670-3).

Claim 119 is also directed to a polynucleotide encoding a mitochondria protein, preferably a humanin (the elected species). As an initial matter, it is noted the specification as filed does not mention the humanin protein. Hence, the disclosure relies on the knowledge of the art at the time of the filing date concerning what was known about humanin. The combined teaching of *Yang* in view of *Balzan* teaches a general tool for delivery of a heterologous mitochondria protein, but not specifically humanin.

Hashimoto supplemented *Yang* in view of *Balzan* by establishing it was known in the art that humanin may be a protein of therapeutic value. (e.g. the abstract). *Hashimoto* made a plasmid vector comprising Humanin (HN) cDNA, and reported that transfection of neuronal cells with HN cDNA abrogated cytotoxicity by NL-APP, and concluded "HN will contribute to the development of curative therapy of AD, especially as a novel reagent that could mechanistically supplement Ab-production inhibitors".

Maximov supplemented the combined teaching by establishing it was well known in the art that the coding sequence of HN was detected in the mitochondria.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the vector as taught by *Yang* in view of *Balzan* for mitochnoria delivering the humanin with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the vector taught by the combined teaching would have more efficient membrane transfer and subcellular organelle-specific targeting function. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
October 15, 2009